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THERAPY

Luigi Alberto Pini
Arrigo F.G. Cicero

Triptans: the experience of a clinical pharmacologist in clinical practice

L.A. Pini (✉) • A.F.G. Cicero
Clinical Pharmacology Service,
University of Modena and Reggio Emilia,
Via del Pozzo 71, I-41100 Modena, Italy
e-mail: pinila@unimo.it
Tel.: +39-059-4224065
Fax: +39-059-4224069

Abstract Despite the pharmacokinetic differences among triptans and the variety of ways of administration, the clinical differences in every day use of these drugs lack in an accepted decisional tree. In fact, there are a number of comparative trials showing conflicting results with regard to efficacy, onset of action, safety and recurrence incidence. That means that the patient's preference probably is the main criterion for choosing one triptan vs. others. This point of view is probably correct considering also that the main cause of therapy failure is non-compliance. A good migraine care strategy requires a balance in what the patient views as satisfactory, a reasonable compromise between efficacy and tolerability, and a careful follow-up. Improvement in compliance should be the main and more immediate goal for the treatment of migraine attacks.

Key words Triptans • Clinical practice • Pharmacology

Migraine is a paroxysmal disorder characterised by attacks of headache eventually associated with nausea, vomiting, photophobia, phonophobia, and malaise. A fast-growing, new class of anti-migraine drugs has recently been introduced for the treatment of migraine: the serotonin (5-HT) 1B/1D agonists. Since the introduction of the first representative, sumatriptan, in 1983, several new compounds of this class have been or are about to be approved for clinical use.

The main pharmacokinetic characteristics of triptans are reported in Table 1 [1]. All the triptans are effective in a high proportion of patients with recurrent migraine attacks, but from the clinical perspective consistency of response, sustained response and good tolerability are the areas that may better clinically distinguish among individual triptans [2]. Michel D. Ferrari, in a review on migraine in *The Lancet* in 1998, defined the "future" problem of choice among the new triptans as the "triptans war" [3]. In fact, comparative literature data are often hard to understand because of lack of standardised measures of efficacy and safety for different doses, different ways of administration and different times from the administration [4]. Besides, few comparative studies have been carried out with triptans other than sumatriptan, almost always taken as a reference (Fig. 1). Indirect comparisons such as meta-analyses only serve as estimates of relative efficacy or safety that cannot substitute the potential usefulness of direct comparative research on a wide population. Moreover, few long-term efficacy and safety studies have been published [5].

Table 2 reports the main pharmacoepidemiological parameters that are needed to evaluate the efficacy and safety of triptans [6, 7]. Compliance may be defined as the extent to which a patient's behaviour conforms to medical advice [8].

Table 1 Pharmacokinetics of oral triptans. (Modified from [1])

Triptan	T_{max} (h)	C_{max} (ng/ml)	F (%)	$t_{1/2}$	AUC (mg/l h)	Metabolism
Sumatriptan						
50 mg	2	31	14	2	118	MAO
100 mg	1.5	54	14	2	158	MAO
Rizatiptan						
5 mg	1.2	7.8	38	1.4	17.4	MAO-A
10 mg	1	19.8	40	2	50	MAO-A
Zolmitriptan						
2.5 mg	2	3	46	2.6	17	P450/MAO-A
Naratriptan						
2.5 mg	2	12.6	74	5.5	98	Renal/CYP450
5 mg	2	23.9	68	5.3	200	Renal/CYP450
10 mg	1.5	46.1	68	5.5	387	Renal/CYP450
Eletriptan						
40 mg	1.8	82	50	5.3	670	CYP450
80 mg	1.4	246	50	6.3	1661	CYP450
Frovatriptan						
2.5 mg	3	7	29.6	25.7	94	CYP450
40 mg	5	53.4	17.5	29.7	881	CYP450
Almotriptan						
12.5 mg	2.5	3	49.5	3.1	80	CYP450/MAO-A
25 mg	1.46	103	69	3.19	558.5	CYP450/MAO-A

AUC, area under the curve; *MAO*, monoamine oxidase; T_{max}, time to maximum concentration; C_{max}, maximum blood concentration; *F*, bioavailability

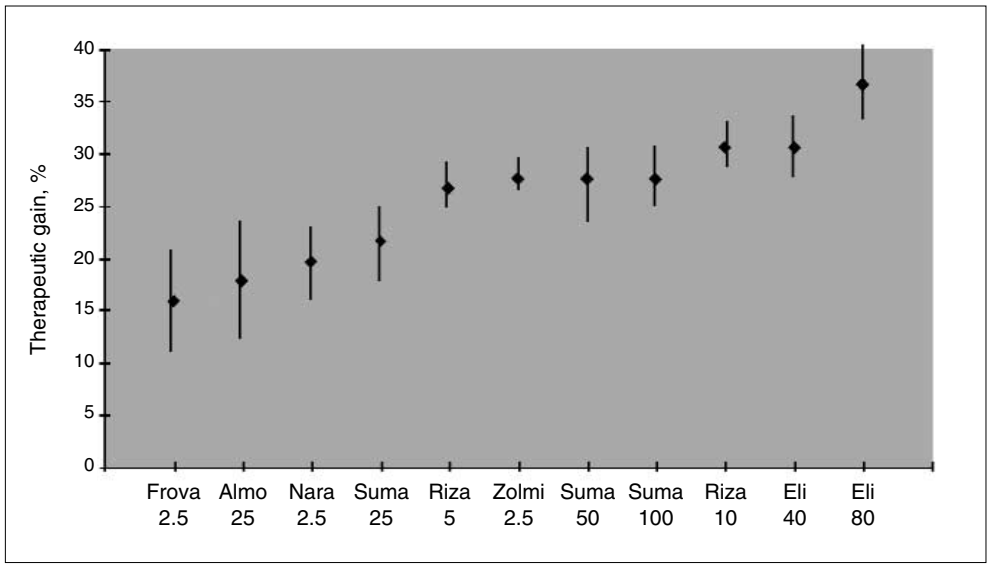

Fig. 1 Comparison of mean therapeutic gain (±SD) with different triptans. *Frova*, frovatriptan; *Almo*, almotriptan; *Nara*, naratriptan; *Suma*, sumatriptan; *Riza*, rizatriptan; *Zolmi*, zolmitriptan, *Eli*, elitriptan. (Modified from [1])

A primary reason for poor compliance among patients receiving medications for headache is adverse effects, many of which are dose related. One difficulty is that triptans often causes adverse effects at therapeutic doses. Some risk factors for adverse effects that have been proposed include age [9], number of drugs the patient is receiving [10] and factors that alter drug distribution or metabolism, such as renal or hepatic insufficiency, congestive heart failure, anaemia, and alcoholism [11]. It has also been suggested that a patient who is receiving specific drugs or drugs of a certain class may be prone to having an adverse effect; however, few studies on headache patients are available (Table

Table 2 Clinical efficacy and safety parameters necessary to compare triptans

Efficacy parameters
Therapeutic gain = Response rate in treated subjects/Response rate in control group
Relative benefit increase = Therapeutic gain/Response rate in control group
Number needed to treat = 100/Therapeutic gain
Safety parameters
Absolute risk increase = Adverse effects (AEs) rate in treated subjects/AEs rate in control group
Relative risk increase = Absolute risk increase/AEs rate in control group
Number needed to harm = 100/Absolute risk increase

3). Comparing effective dose sizes, triptans seem to differ in their capacity to cause adverse effects without any relationship between adverse effect frequencies and absolute dose size, logD, or absolute dose-size lipophilicity index (ADLI = absolute dose in mg/LogD). Moreover, because of the triptans' similar high affinity for the 5-$HT_{1B/1D}$ receptors, adverse effects could be mediated through mechanisms that are unrelated to the intrinsic efficacy at those receptors [12].

In clinical practice, the choice of a triptan depends on a number of factors. First of all, it must be decided to use a triptan instead of another non-specific painkiller medicine.

At the moment a stratified approach for migraine attack therapy is preferred to optimise positive reinforcement due to the efficacy of the therapy; triptans are able to reduce the number of non-responders to usual therapy [13]. In clinical practice, the differences outlined (sometimes with conflicting results) in comparative clinical trials are immediately undetectable, so that the efficacy or safety of different triptans is in many case overlapping for the clinician. In this situation the main point to consider in choosing triptans seems to be the patient's preference. In fact, the difference in direct costs, in Italy, are almost negligible, and the difference in preference by patients can be resumed as the following:

1. Rapidity in onset of action;
2. Consistency in repeated use;
3. Mode of administration;
4. Previous use;
5. Incidence of side effects;
6. Counselling of other patients.

Keeping in mind this point, we can identify the more acceptable drug, optimise the compliance and hope to target the maximum therapeutic effect. A well-informed patient is the first step for a good therapeutic strategy.

In conclusion, the most frequent question is: Which is the best triptan? The best answer to this question is that it is the wrong question! In fact, a patient's expression of treatment reference is a valuable thing to know, not only for the individual's clinical management, but also at the population level for epidemiological and economic reasons. In agreement with Sheftell and Fox [14], we believe that a good migraine care strategy requires a balance with what the patient views as satisfactory, a reasonable compromise between efficacy and tolerability, and a careful follow-up.

Table 3 Comparison of adverse effects and recurrence with different triptans. Data refer to oral administration unless otherwise indicated

Drug	All AE, %	Chest symptoms, %	Recurrence, %
Placebo	29–46	1–3	10–44
Sumatriptan			
100 mg	58	5	34
50 mg	56	5	34
Rectal	2	0	22
6 mg SC	59	5	46
Naratriptan			
5 mg	18	0.2–1.0	32
Zolmitriptan			
2.5 mg	39	3	26
Rizatriptan			
5 mg	39	2	38
10 mg	31–47	5	41
Almotriptan			
12.5 mg	46	0.4–2.0	18
Elitriptan			
40 mg	NR	7	21
50 mg	NR	7	32

SC, subcutaneous; *AE*, adverse events; *NR*, not reported

References

1. Saxena PR, Tfelt-Hansen P (2000) Triptans, 5-HT1B/1D receptor agonist in the acute treatment of migraine. In: Olesen J, Tfelt-Hansen P, Welch KMA (eds) The Headaches, 2nd edn. Philadelphia
2. Diener HC, Kaube H, Limmroth V (1999) Antimigraine drugs. J Neurol 246(7):515–519
3. Ferrari MD (1998) Migraine. Lancet 351(9108):1043–1051
4. Diener HC, Limmroth V (1999) Acute management of migraine: triptans and beyond. Curr Opin Neurol 12:261–267
5. Salonen R (2000) Drug comparisons: why are they so difficult? Cephalalgia 20(S2):25–32
6. – (1999) ABC degli studi clinici. Sperimentazioni controllate e randomizzate (RCTs). Bollettino d'Informazione sui Farmaci. 6:5–9
7. – (2000) Glossario dei termini più frequentemente usati per riportare i risultati di un trial o di una metanalisi. Bollettino d'Informazione sui Farmaci 7:1–2
8. Alderman MH, Madhavan S, Cohen H (1996) Antihypertensive drug therapy: the effect of JNC criteria on prescribing patterns and patient status through first year. Am J Hypertens 9:413–418
9. Hanlon JT, Schmader KE, Koronoswki MJ et al (1997) Adverse drug events in high risk older outpatients. J Am Geriatr Soc 45:945–948
10. Colley CA, Lucas LM (1993) Polypharmacy: the cure becomes the disease. J Gen Intern Med 8:278–283
11. Cullen DJ, Sweitzer BJ, Bates DW, Burdick E, Edmonson A, Leape LL (1997) Preventable adverse drug events in hospitalised patients: a comparative study of intensive care units and general care units. Crit Care Med 25:1289–1297
12. Fox AW (2000) Comparative tolerability of oral 5-$HT_{1B/1D}$ agonists. Headache 40:521–527
13. Pini LA, Fabbri L, Cavazzuti L and The Sumatriptan 50 mg Italian Study Group (1999) Efficacy and safety of sumatriptan 50 mg in patients not responding to standard care, in treatment of mild to moderate migraine. Int J Clin Pharmacol Res 19:57–64
14. Sheftell FD, Fox AW (2000) Acute migraine treatment outcome measures: a clinician's view. Cephalalgia 20(S2):14–24